Small Pharmaceutical Business Educational Forum

FDA IRB & Informed Consent Regulations

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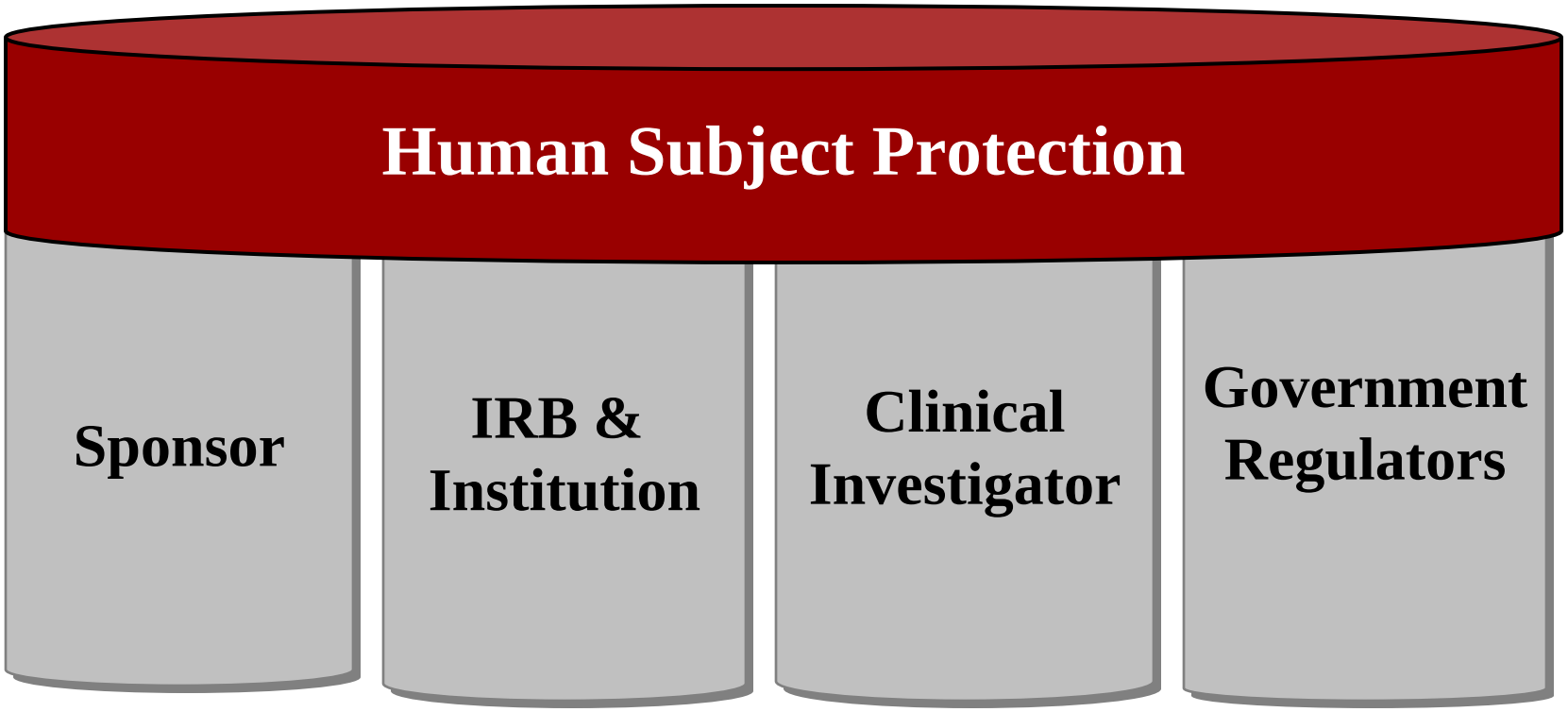
Overview

- Background
- Basic ethical principles underlying HSP regulations & research
- IRB and Informed consent regulations
- Subpart D
- IRB Registration Rule
- Inspection do's and don'ts
- Reporting Unanticipated Problems

Partnership



IRB/IC Regulations are two important components of human subject protections, but there are many FDA regulations and activities that positively affect human subject protections (e.g. scientific reviews, trial registries etc…)

Human Subject Protections Overview

- ***Before*** initiation of the clinical investigation
  - FDA review of IND (30 days)
  - IRB review and approval
  - Informed consent
  - Data Monitoring Committee and plan (as needed)
  - GCP
  - GLP
  - GMP

Human Subject Protections

- ***During*** the clinical investigation
  - FDA review of changes and AER
  - IRB continuing review, AER
  - Informed consent process
  - Data monitoring committee
  - GCP
  - DSI Inspections: IRBs, CIs
    - Evaluate data integrity
    - Inspect and assess adherence to protocol, amendments, investigator's brochure, and informed consent
    - Inspect and assess conduct of the clinical investigators and IRBs
    - Routine/surveillance and For-cause/directed inspections

Human Subject Protections

- ***After*** completion of the clinical investigation
  - FDA review (e.g., annual reports, study reports, NDA review, additional studies, labeling)
  - GLP
  - GMP
  - DSI Inspections
    - Retrospective focus on data integrity, trial records, and IRB documentation
  - Study registry and results: improved transparency

Background Behind IRB & IC Regulations

- Nazi Experimentations
- Tuskegee Syphilis Experiment –lead to Belmont Report
- 1966: Henry Beecher published a review of 22 unethical studies conducted by well-reputed CI and published in well-respected journals

Tuskegee Syphilis Experiment

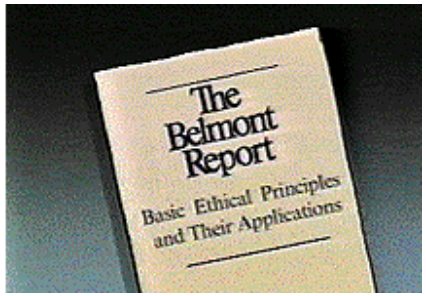
- 1932-1973: Observational study of the effects of untreated syphilis
- 1943: Treatment for syphilis becomes available but withheld
- 1966: Beecher's article creates awareness of event
- 1972: US Senate Hearings on human experimentation
- 1973: Study stopped; men and their families treated
- 1978: National Commission for the Protection of Human Subjects of Biomedical/Behavioral Research formed
- 1997: President Clinton apologizes for the Tuskegee study

Lasting effects include deep-rooted mistrust of researchers.

Trust is fundamental to research; once lost it is nearly impossible to regain.

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research



The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

The Belmont Report Principles

- **Respect for Persons**
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- **Beneficence**
  - Maximize benefits and minimize harms
- **Justice**
  - Equitable distribution of research costs and benefits

Each of these are reflected in the regulations!

Ethical Framework for Regulations/Research

- **Respect for persons**
  - Informed consent, consent of LAR, assent
  - Additional protections for vulnerable subjects
- **Beneficence**
  - Risks to subjects are reasonable in relation to anticipated benefits
  - The R/B ratio is at least as favorable as available alternative approaches
- **Justice**
  - Selection of subjects is equitable

FDA Regulations

- Goal: Implement the National Commission's recommendations
- 1981: 21 CFR Part 50 (Informed Consent Regulations)
- 1981: 21 CFR Part 56 (IRB Regulations)
  - Subpart A: General provisions
  - Subpart B: Organization and Personnel
  - Subpart C: IRB Function and Operations
  - Subpart D: Records and Reports
  - Subpart E: Administrative Actions for Noncompliance
- 2001: 21 CFR Part 50, Subpart D – Additional Safeguards for Children in Clinical Investigations

What is an IRB?

21 CFR 56.102(g)

- Any board or other group formally designated by an institution to review research involving human subjects
- Primary purpose is to assure the protection of the rights and welfare of the human subjects

Commercial vs. non-commercial IRBs: the balance between competing priorities need to be considered: profit motive not unique to commercial entities.

Institutional Responsibilities

- Designate one or more IRBs to review and approve all FDA-regulated research
- Provide sufficient space and staff to support the IRB's review and record-keeping duties
- Ensure that there is an institutional environment that promotes the ethical conduct of research
- Ensure the IRB is so situated to command respect for its advice and decisions

IRB Membership (21 CFR 56.107)

- At least five members of varying backgrounds
  - Sufficiently qualified
  - Not solely of one profession
  - Gender diversity
- At least one non-scientist and one non-affiliated member
- Expertise with "vulnerable populations" if the IRB reviews research involving these populations
- Outside consultants as needed

Conflicted person does not need to leave the room but can't vote: minutes should reflect that they did not vote!

FDA does not prohibit compensation/payment for IRB members although it should not be contingent on approvals

R.N.s are not considered non-scientists

IRB Review Responsibilities (21 CFR 56.109)

- Review and approve, require modifications, or disapprove all covered research
- Require that informed consent is in accordance with regulations
- Require documentation of informed consent or may waive documentation in accordance with regulations
- Notify investigators in writing of decisions
- Conduct continuing review of research at intervals appropriate to the degree of risk but not less than once per year

Notification of CI must be in writing

IRB Functional Responsibilities (21 CFR 56.108)

- Follow written procedures for:
  1. Conducting initial and continuing review and reporting findings/actions to CI and the institution
  2. Determining which projects require review > annually and which need verification from other sources that no material changes have occurred
  3. Ensuring prompt reporting to the IRB of changes to research
  4. Ensure changes in research not initiated without IRB review and approval (unless when needed to eliminate an immediate hazard)
  5. Reporting of unanticipated problems
  6. Reporting serious or continuing noncompliance with the regulations or requirements of the IRB
  7. Reporting any suspension or termination of IRB approval for research
  8. Determining SR/NSR for device studies

Consider others: pediatric risk determination, review of HUDs, etc…

Criteria for IRB Approval (21 CFR 56.111)

1. Risks to subjects are minimized
2. Risks are reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent is sought from each subject/LAR
5. Informed consent is appropriately documented

When appropriate:

6. Data collection is monitored to ensure subject safety
7. Privacy and confidentiality of subjects is protected
8. Additional safeguards are included for vulnerable populations

This is the floor, not the ceiling

IRB Records (21 CFR 56.115)

- Copies of research documents
- IRB meeting minutes
- Records of continuing review activities
- Correspondence with CI
- IRB roster
- Required Written Procedures
- Statements of significant new findings provided to subjects

Retain for 3 years after completion of study

Regulations do not require public/sponsor access to IRB records

IRB Meeting Minutes (56.115(a)(2))

- Attendance at the meetings
- Actions taken by the IRB
- Vote on these actions including the number of members voting for, against, and abstaining
- Basis for requiring changes in or disapproving research
- Documentation of specific findings required by the regulations
- Written summary of the discussion of controverted issues and their resolution

Quorum = Half + round up; no proxy votes/ad-hoc substitutes; pre-designated alternate IRB members permitted.

Exempt Research (21 CFR 56.104)

- Emergency use of a test article, provided that it is reported to the IRB within 5 working days. Any subsequent use of the article at the institution is subject to IRB review.
- Taste and food quality evaluation and consumer acceptance studies
- Certain research prior to July 27, 1981

"Subsequent use" is 2nd use so IRB should consider the possible need for subsequent use after the 1st use reported. Caveat: use common sense; don't deny emergency treatment when needed

Expedited Review (21 CFR 56.110)

- An IRB may use expedited review for
  - Research found on "the list" and
  - Found to (1) presents ≤ minimal risk, AND/OR (2) involves minor changes in previously approved research
- Carried out by IRB Chair OR one or more experienced IRB members designated by the Chair
- Reviewer can exercise all of the authorities of the IRB except disapproval
- Full IRB must be informed of research approved under expedited review

Don't forget to inform IRB of activities

Expedited review can not over-ride IRB decisions

Expedited Review List

- Studies of drugs/devices if IND/IDE not required; or a device if approved for marketing & used as such
- Collection of blood samples by finger sticks, heel sticks, ear sticks or venipuncture (restrictions on age, weight, and volume)
- Prospective collection of biological specimens for research purposes by noninvasive means
- Collection of data through noninvasive procedures routinely employed in clinical practice
- Research involving materials that have been collected, or will be collected solely for nonresearch purposes
- Collection of data from voice, video, digital or image recordings made for research purposes

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Expedited Review List (cont.)

- Research on individual or group characteristics or behavior or research involving survey, interview, oral history, focus group, program evaluation, etc..
- Continuing review of research where
  - (i) the research is permanently closed to the enrollment of new subjects;
  - (ii) all subjects have completed all research-related interventions; and
  - (iii) the research remains active only for long-term follow-up of subjects; or
  - Where no subjects have been enrolled and no additional risks have been identified; or
  - Where the remaining research activities are limited to data analysis
- (Not under IND or IDE) where the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

Is an IND/IDE required?

- Devices
  - 240-276-4040
- Drugs
  - 301-796-3400
- Biologics
  - 301-827-2000
- Uncertain
  - 301-827-1685

Full Review

- Convened meeting

  Primary reviewer process okay; however all members should receive ICD and a protocol summary and have access to all documents

- Quorum
  - Simple majority of IRB members required (half plus 1)
  - At least one non-scientist present
  - Approval by simple majority of those present

No proxy attendees/votes

If quorum fails during a meeting (early departures, loss of non-scientist), no further votes can be taken until quorum restored

Continuing Review (21 CFR 56.109(f))

- Appropriate to the degree of risk and not less than once per year
- Determining continuing review date should be described in IRB Written Procedures (56.108)
- This regulation also provides the IRB with the authority to observe or have a third party observe the consent process and the research

CR should be substantive and meaningful

Don't forget to follow your written procedures (e.g. send out reminders to CI; actions against non-complaint CIs as written)

Recommended Materials for CR

- Latest version of the protocol and ICD
- Any proposed modifications to the protocol or ICD
- Written summary of changes and a status report on the progress of the research to include:
  - Number of subjects
  - Description of any AE or UP involving risks to subjects or others
  - Summary of withdrawal of subjects from the research
  - Any complaints about the research
- Any new information relevant to human subjects, especially risks associated with the research
- Any other critical information such as reports from the DMC

Multi-Center Research

- Central IRB Review Reduces duplication of effort
  - 21 CFR 56.114 – Cooperative Research:
    - Allows joint review
    - Reliance on the review of another qualified IRB
    - Other similar arrangements
- "Local" IRB may delegate all, some, or none of its responsibilities to the Central IRB; document agreements in written memorandum of understanding

Informed Consent: Basic Elements

(21CFR 50.25(a)) required statements/disclosures

1. Study involves research
   - Purpose
   - Expected duration
   - Description of procedures/experimental components
2. Reasonably foreseen risks or discomforts
3. Reasonably foreseen benefits to the subject or to others
4. Appropriate alternatives
5. Confidentiality/FDA may inspect
6. Compensation in general and for research-related injury
7. Point of contact for questions
8. Participation is voluntary

Don't forget a statement about the possibility of FDA inspection

Payment to subjects should not create undue influence

Screening procedures such as wash-outs and eligibility tests require consent

Balanced discussion on risks/benefits

Informed Consent: Additional Elements

(21 CFR 50.25(b)); when appropriate

- The particular procedure may involve unforeseeable risk to the subject (embryo or fetus)
- Circumstances of termination
- Costs to the subject
- Consequences of withdrawal
- Significant new findings may be communicated
- Approximate number of subjects

Exception from Informed Consent

[Unplanned emergency use (21 CFR 50.23)]

- Possible when CI and independent physician certify:
  - Life-threatening situation requiring use of test article
  - Informed consent cannot be obtained from subject or LAR
  - No alternative treatment that is equal or better

  Use must be reported to IRB within 5 days
- Emergency use required to preserve life but no time for a 2nd opinion: requires review by independent physician within 5 days and reported to IRB within 5 days
- President may waive the prior consent requirement for military personnel

Exception from Informed Consent: (Planned) Emergency Research (21 CFR 50.24)

- IRB must find and document the following:
  1. Life-threatening situation
  2. Available treatments are unproven or unsatisfactory
  3. Scientific study necessary to evaluate safety and efficacy
  4. Obtaining informed consent is not feasible
  5. There is the prospect of direct benefit to the subject
  6. The investigation could not practicably be carried out w/o waiver
  7. Therapeutic window defined and CI commits to contacting LAR
  8. An ICD c/w with §50.25 is available
  9. Additional protections required: Community consultation, Public disclosure, DSMB
  10. Procedures in place to inform LAR/family/subject ASAP

Requires a lot of thought and by nature will be controversial so document!

Informed Consent Documentation

(21 CFR Part 50.27)

- Reviewed & approved by IRB
- Signed and dated by subject or LAR
- Copy must be provided to subject
  - Long form contains all elements of IC; or
  - Short form states information was presented orally
    - Need a witness to presentation
    - IRB review & approval of written summary of oral presentation
    - 3 signatures:
      - Witness signs form & summary
      - Person obtaining consent signs summary
      - Form is signed by the subject or LAR

Rarely a problem during IRB inspections

Informed Consent Documentation

[21 CFR 50.27, 21 CFR 56.109(c)]

Informed consent must be signed and documented in written form unless waived by the IRB under two conditions:

- IRB finds that the research presents:
  - No more than minimal risk; and
  - Involves no procedures for which written consent is normally required

or

- IRB finds that the research meets the requirements found under 21 CFR 50.24.

Verbal/telephone consent not acceptable however fax signed copy from LAR acceptable

Additional Protections for Children

[21 CFR 50 Subpart D]

Categories of Research (based on risk and benefit)

- **50.51:** Not involving greater than minimal risk (i.e., no benefit is possible)
- **50.52:** Involves greater than minimal risk but presents the prospect of direct benefit to individual subjects (i.e., generally treatment protocols)
- **50.53:** Involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (i.e., class studies)
- **50.54:** Not otherwise approvable [by the IRB] which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (i.e., no risk cap/no benefit to subject)

Required IRB Findings

- 50.51:
  - Risk ≤ minimal risk
- 50.52
  - Risk is justified by anticipated benefit to the subject
  - Risk/benefit of research is ≥ available alternative approaches
- 50.53
  - Risk represents a minor increase over minimal risk
  - Interventions/procedures reasonable commensurate with actual or expected medical, dental, psychological, social, or educational situations
  - Likely to yield generalizable knowledge that is of vital importance relative to the disorder

Required IRB Findings

- 50.54
  - IRB does not believe it can approve the research under the other categories
  - Presents a reasonable opportunity to further the understanding of serious problems affecting the health/welfare of children

  [Refer to the FDA for review by a panel of experts and an opportunity for public review and comment]

For all categories:

- IRB must determine that adequate provisions for child assent and parental/guardian permission have been made
- Special consideration for Wards (see 21 CFR 50.56)

Child Assent

[21 CFR 50.55]

- IRB must determine that adequate provisions are made for soliciting assent when in the judgment of the IRB the children are capable of providing it based on:
  - Age (Most IRB's require investigators to seek the assent of children > 7 y/o)
  - Maturity
  - Psychological state
- Assent not required if IRB determines:
  - Capability of some (or all) of the children is so limited that they can not be reasonably consulted
  - The research hold out the prospect of direct benefit that is not otherwise available.

Child Assent

[21 CFR 50.55]

- IRB may waive assent requirement if it finds and documents that:
  - Involves no more than minimal risk to the subjects
  - Will not adversely affect the rights of the subjects
  - Could not practicably be carried out without the waiver
  - Whenever appropriate the subjects will be provided with pertinent information after participation
- State Law needs to be considered:
  - Emancipated minor: may be eligible to give consent due to a variety of circumstances-judicial decree, marriage, parenthood, living independently, self-supporting, service in the armed forces

Parental Permission

[21 CFR 50.55]

- Parental permission cannot be waived except 21 CFR 50.23 and 21 CFR 50.24
- One parent sufficient for 50.51/50.52
- Both parents required for 50.53/50.54 (unless one is deceased, unknown, incompetent, not reasonably available, or has no legal responsibility)
- Need to consider State Law
- Must be documented like consent

New!
IRB Registration

- Mandates IRBs to register through a system maintained by HHS
- Goals:
  - Identification of IRBs for inspections
  - Disseminating information to IRBs such as educational materials, new regulations and guidance
  - Improved transparency of trial oversight
- Compliance required by September 14, 2009
- Register electronically at http://ohrp.cit.nih.gov/efile

We will be evaluating compliance in our FY10 inspections

IRB Registration

- Required Elements
  - Name and contact information of senior officer responsible
  - IRBs name and contact information
  - Chairman name and contact information
  - Approx. number of active FDA studies during preceding 12 months
  - Description of types of FDA products covered (drugs, devices, biologics etc…)

- If already registered with OHRP: update data to reflect FDA related work

IRB Registration

- Must be updated at least every 3 years; sooner if:
  - Change in contact or chairman: 90 days
  - Change in status of review type (e.g. drug, devices etc…): 30 days
  - IRB disbands: 30 days
- Change in volume of work can be updated every 3 years
- Technical problems:
  - http://www.hhs.gov/ohrp/daqi-staff.html

IRB registration is not an FDA endorsement of IRB competency or expertise

IRB Inspections

- Purpose: To determine if IRBs are operating in compliance with FDA regulations (reflect statutory requirements) and IRB written procedures
- Categories
  - Routine Surveillance
  - For-Cause
  - OAI Follow-up* (receiving higher priority than in the past)
  - Vulnerable populations (e.g. Children/Subpart D)
- Process
  - Pre-announcement
  - Opening Interview (Issue Form FDA 482 and present credentials)
  - Inspection
  - Closing Meeting/Exit Interview (Issue Form FDA 483)

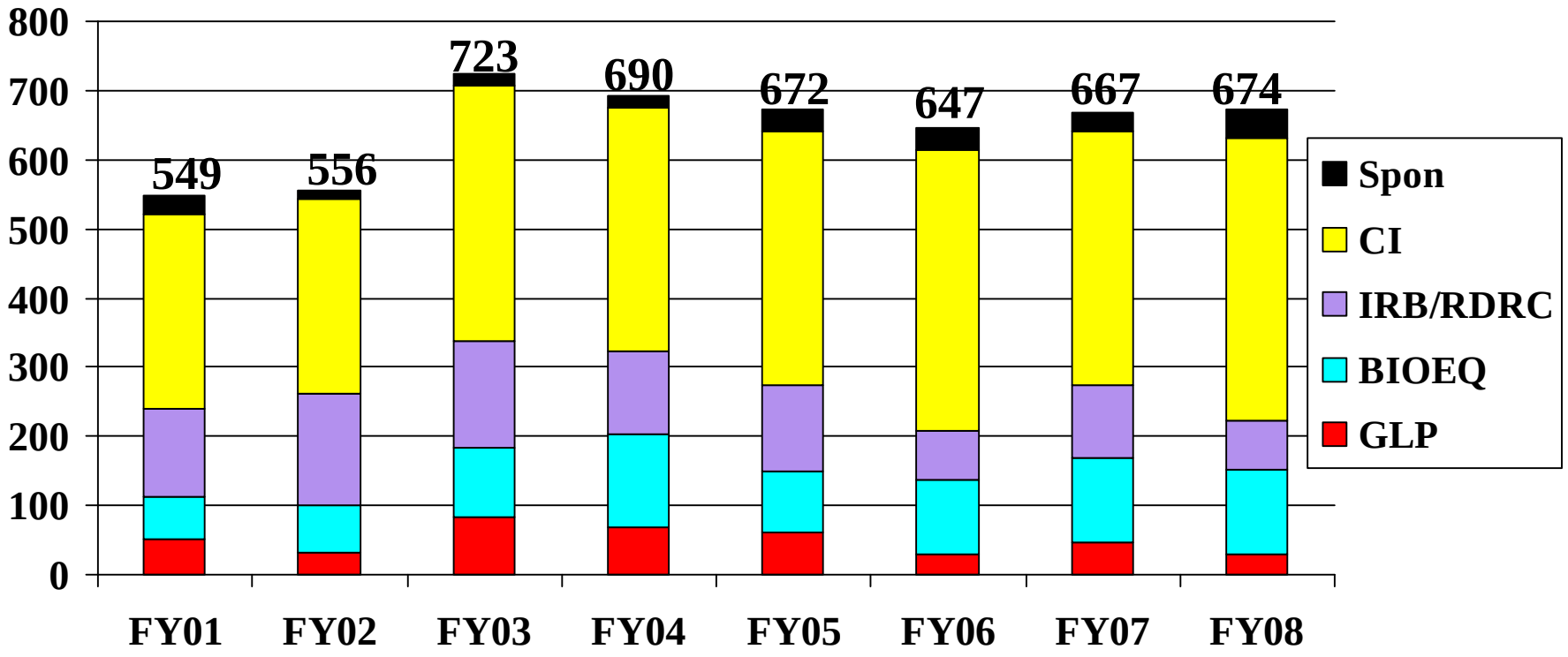
IRB Inspections

- Possible Outcomes
  - NAI
  - VAI
  - OAI (with and without restrictions)
  - Disqualification (21 CFR 56.121)
- Possible restrictions include
  - No new studies
  - No new subjects to ongoing studies
  - Terminate ongoing studies
  - Notify interested parties of deficiencies (Sponsors, State Agencies, other Federal Agencies etc…)

BIMO Inspections

- Each FDA Center has oversight of inspections of research related to the product(s) it regulates
- Inspections are usually conducted by Office of Regulatory Affairs field investigators
  - Field inspectors are NOT specifically assigned to CDER
  - All Field inspectors are responsible for conducting inspections for all centers (CBER, CDER, CDRH, CFSAN, etc.)

CDER BIMO Inspections FY 2000-2008



IRB Inspections

- Federal requirements are minimum requirements
- FDA has traditionally viewed IRBs as allies
- Common goal: To protect the rights and welfare of human subjects
- We seek compliance through cooperation and education
- Inspections conducted by ORA
- Categories of findings:
  - NAI
  - VAI
  - OAI
  - Untitled

IRBs are encouraged to provide written responses to findings

Common Problems

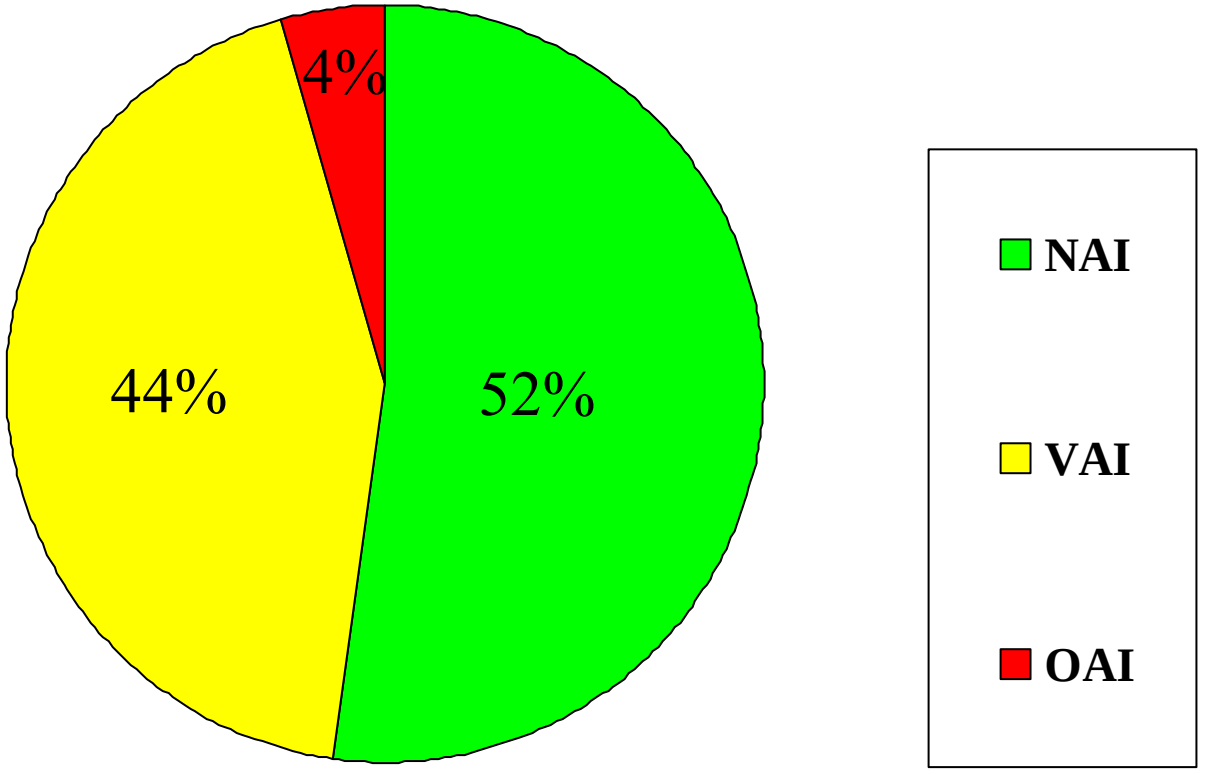
- Written Procedures
  - Missing or Inadequate
  - Not following them
- Documentation of IRB activities (recordkeeping): e.g., not maintaining complete files//missing correspondence//voting not clear//inadequate minutes
- Continuing Review done late
- Quorum (half + round up)
- Membership (non-scientist, non-affiliated etc...)
- Expedited Review - inappropriate use
- ICD – missing elements//not using the most recent version

IRB Inspections

- How to survive
  - Best to have an IRB member present (preferably the Chair)
  - Ensure record available
  - Have all SOPs/Written Procedure available
  - IRB Membership Rosters (current and past)
  - List of completed and ongoing studies
  - Organized study files with documents reviewed, correspondences to CI, AE reports, progress reports, protocol violations etc…
  - At exit interview don't miss the opportunity to respond to all findings and follow this up with a written response.

Consider inspections an opportunity to learn; inspectors have a tremendous amount of experience in which to benefit from.

IRB Classifications
CDER Inspections – FY08



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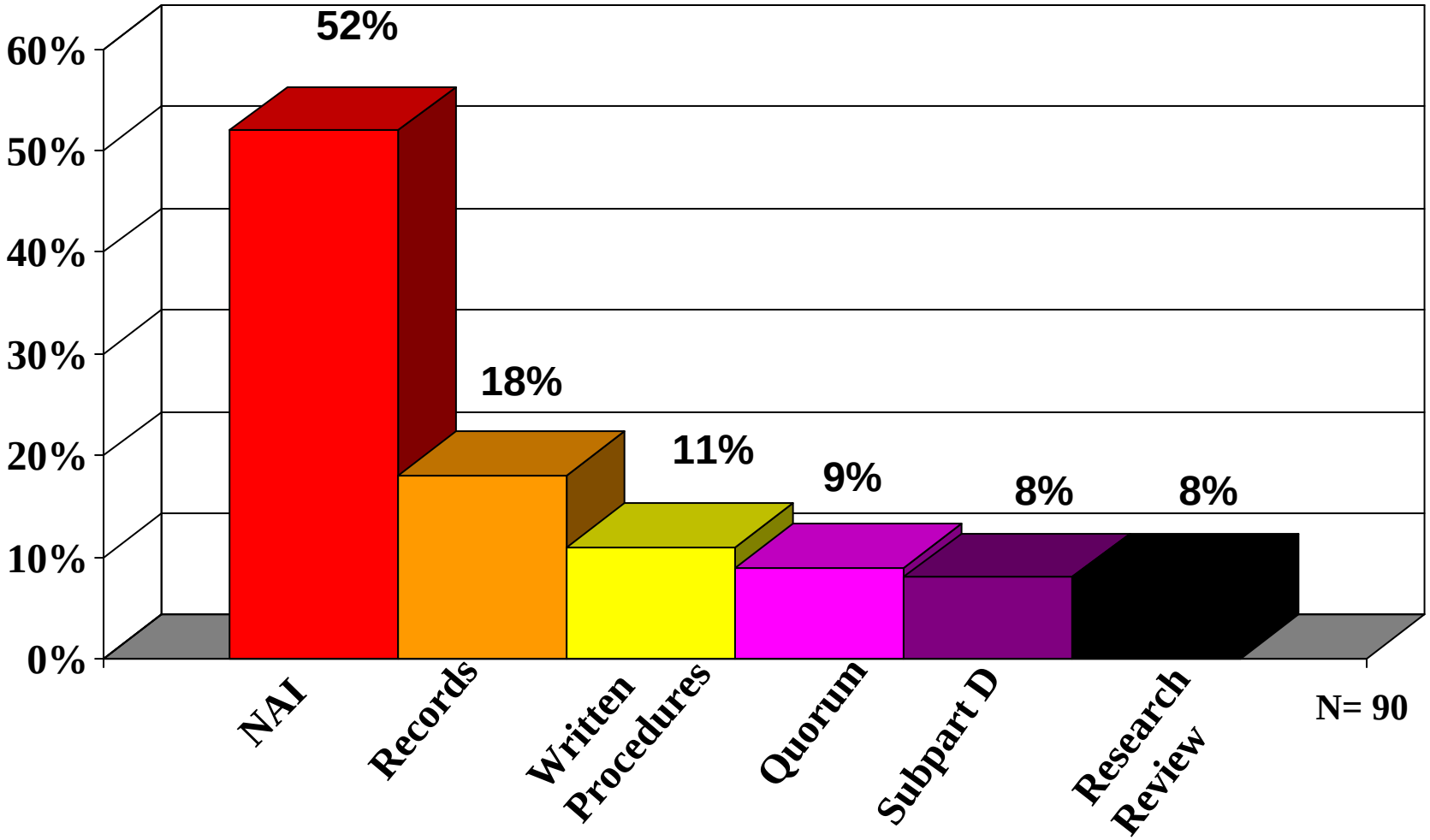
IRB Inspection Classifications FY07-09

FY	Field Class NAI	Field class VAI	# of Field Class OAI
07	61%	33%	6%
08	51%	43%	6%
09	42%	47%	11%*

* FY09 data incomplete

IRB Deficiencies FY08: CDER



2008 Top Ten: VAI

1. Meeting minutes without sufficient details (attendance, actions etc.)
2. Failure to follow written procedures
3. Failure to maintain list of IRB members
4. Quorum related issues
5. Informed consent documents lacking required elements
6. Failure to maintain copies of all research proposals reviewed
7. Subpart D related issues (usually not categorized)
8. Inappropriate use of expedited review
9. Failure to excuse IRB member with conflict
10. Failure to inform IRB of research approved by expedited review

Top Ten: OAI

- Essentially the same as VAI
- Considerations include:
  - Systemic vs. isolated event
  - Public health impact
  - Past inspectional history; (e.g. repeated observations – fail to fix)
  - The robustness of the written response
- Examples of egregious problems:
  - No written procedures
  - ICD consistently lack required elements
  - CR dates consistently and substantially not met
  - Consistent misuse of expedited review
  - Consistently lack quorum or repeatedly allow conflicted IRB member to vote
  - Repeatedly failed to maintain adequate records
  - Occasionally: behavior that results in referral to Office of Criminal Investigation (e.g. falsification of records, administrators ignoring the actions of the IRB)

OAI Inspection Outcomes

- Possible outcomes
  - Warning letter requiring written response
  - Warning letter with restrictions (e.g. no new subjects, no new studies, no use of expedited review etc…)
  - Disqualification
  - All Warning letters are posted
- OAI Follow up inspections approximately 1 year
  - To assess actions taken in response to 483/WL
  - May look at entire operations
  - Repeated observations may lead to escalating actions

IRB Reporting Responsibilities

- Follow written procedures for ensuring prompt reporting to the IRB, institution, and the FDA of any
  - **UP involving risks to human subjects or others**
  - Any instance of serious or continuing non-compliance
  - Any suspensions or terminations of IRB approval

- What needs to be reported
  - **UP involving risk**
  - Any AE caused by or probably caused by the drug; alarming
  - New observations related to safe use
  - AE…serious and unexpected
  - New findings from lab animals suggesting a significant risk
  - Unexpected fatal or life-threatening experience
  - Unexpected serious harm
  - Unanticipated adverse device effects

FDA Guidance: Adverse Event Reporting to IRBs – Improving Human Subject Protection

- Issued January 2009
- Goal: To improve the efficiency in which adverse events/unanticipated problems are reported to IRBs

Definitions:

Unanticipated Problems:

- Not defined in FDA Regulations but in general should only be considered an UP if it were unexpected, serious, and would have implications for the conduct of the study (e.g. requires significant safety change in protocol, Investigator Brochure etc…)

Guidance: An individual AE ordinarily does not meet these criteria because as an isolated event its implications for the study cannot be understood

How to Determine if an AE is an Unanticipated Problem

1. Is it a problem that involves risks to subjects or others?
2. If yes:
   - Is it previously known (i.e. in CIB, ICD etc…)
   - If known, does it occur at a frequency greater than expected
   - If known, does it occur at a severity greater than expected

Examples of Unanticipated Problems

- A series of adverse events that on analysis is both unanticipated and a problem for the study.
- An AE that is described in the study documents as expected but that occurs at a greater frequency or severity than expected.
- Any AE that represents a serious unexpected adverse event that is rare in the absence of drug exposure.
- Any other AE event that would cause the sponsor to modify the CIB, protocol or ICD.

i.e. UP are generally events not previously observed, not listed in the CIB or not consistent with the known risk information about the drug. They can also include events that are more severe or more frequent than expected. Generally should represent only a small fraction of AEs in most trials.

FDA Guidance

- The PI and the sponsor should give careful consideration of whether an AE is an UP that must be reported to the IRB.
- General rule: Determining whether an isolated AE occurring at a local site is an UP can often only be understood after an analysis of aggregated data across multiple study sites (best done by Sponsor or DSMB).
- Major exceptions to this rule include isolated serious AEs that are uncommon and strongly associated with drug exposure (e.g. angioedema, anaphylaxis, and Stevens Johnson syndrome).

FDA Guidance: What must be reported

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (e.g. Stevens Johnson syndrome)
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g. tendon rupture).
- Multiple occurrences (i.e. require aggregate data analysis) that is determined to be an UP.

FDA Guidance: What must be reported

- An AE that is described in study materials but occurs at a specificity or severity that is inconsistent with prior experience.
- A serious AE that is described in study materials but the occurrence rate in the study represents a clinically significant higher rate than expected.
- Any other AE or safety finding (e.g. new pre-clinical data) that would cause the sponsor to modify study material or would prompt other actions by the IRB to ensure the protection of human subjects.

UP Guidance Conclusion

- Large volume of unanalyzed individual safety reports is rarely helpful to IRB in its efforts to protect subjects
- Individual AE generally is not considered an UP problem because its implication for the study cannot be understood.
- Sponsor of multicenter trial in best position to analyze data in context and has a requirement to report findings to CI and FDA (safety reports).
- FDA encourages efforts by CI and sponsors to ensure IRBs receive meaningful information on adverse events.

Expanded Access to Investigational Drugs for Treatment Use (Subpart I)

- Formalizes past FDA practices
- FRN: August 13, 2009
- Effective October 13, 2009
- Goal: to improve access for patient with serious and life-threatening diseases/conditions when "no comparable or satisfactory alternative" to diagnose, monitor or treat.
- Requirements: FDA must determine that:
  - Serious or immediately life-threatening; no comparable or satisfactory alternative
  - Potential benefit justifies risk
  - Use won't interfere with investigation leading to market approval
- Describes 3 different scenarios based on # to be treated
- IRB safeguards still apply

Thank you and Questions ?

Resources

- GCP website for IRB Guidance:
  - http://www.fda.gov/oc/ohrt/irbs/default.htm
- Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection:
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf
- 21 CFR Part 50 and 56:
  - http://www.fda.gov/oc/gcp/regulations.html
- Inspection checklist:
  - http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118063.htm
- FDA contacts for reporting:
  - http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ReportProblemstoFDA/ucm136102.htm
- General GCP information:
  - http://www.fda.gov/oc/gcp/
- Policy Questions Mailbox: GCP.Questions@FDA.HHS.GOV

Resources

- Belmont Report:
  - http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm
- Declaration of Helsinki
  - www.wma.net/e/policy/b3.htm
- CIOMS
  - www.cioms.ch/frame_guidelines_nov_2002.htm
- Expedited Review List:
  - http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed
- Guidance on IRB Inspections:
  - http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/UCM118085.pdf
- FRN On IRB Registry:
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/E9-682.htm

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8 down/8 to go!